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Familial Aggregation of Cancer from Proband Cases with Childhood Adrenal Cortical Carcinoma[1]

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Family pedigree of Li-Fraumeni syndrome was investigated from probands with childhood adrenocortical carcinoma in Japan. From 47 probands, 7 families had 3 or more cancer cases at ages less than 45 years within the first generation; one satisfied Li's original criteria, two were acceptable because of multiple primary cancer in the probands, and others showed an aggregation of cancers with onsets at early ages, though no sarcoma of mesenchymal origin was found. A significantly higher occurrence of cancer in the mothers of the probands, especially of the breast, was consistent with reports from the USA, and liver cancer, osteosarcoma and lung cancer among family members under the age of 45 also showed a higher frequency than in the general population. Similarities and differences between Japanese and Caucasian cases are discussed.

Key words: Li-Fraumeni syndrome — Adrenocortical cancer — Breast cancer — Epidemiology

Studies of familial aggregation of cancer have contributed to clarification of the genetic influence upon cancer occurrence.[1,2] Childhood cancer is a good target for genetic study, because the environmental exposure which often hides the effect of genetic or individual susceptibility is considered to be less than that in adults. Hereditary retinoblastoma is a good example of how dominant inheritance is caused by the deletion of the RB gene, which could be related directly to carcinogenesis.[1,3] Loss of heterozygosity of the RB gene has been found to be related to many other cancers, and now RB is recognized as one of the important suppressor genes.[4]

In Li-Fraumeni syndrome and so-called Lynch's sarcoma, breast cancer, lung cancer and adrenocortical cancer (SBLA) syndrome, a complicated accumulation of childhood and adult cancers in one family is usually found, and it is of interest to establish whether or not these various cancers may be caused by a single gene or multiple gene events.[5–8]

The criteria for Li-Fraumeni syndrome and SBLA syndrome have not yet been precisely defined, because of the rather broadly defined concept including various tumors. An alternative name of sarcoma-breast cancer syndrome has been proposed, but it has not yet been widely accepted.[2] Frequency and incidence of this syndrome in different ethnic groups or different countries have not yet been clarified. We tried to confirm whether or not families with Li-Fraumeni syndrome are present in Japan. As the proband, we chose childhood adrenal cortical cancer, because this carcinoma is involved in both Li-Fraumeni and SBLA syndrome and its rarity could exclude cancer aggregation by chance.[9,10]

MATERIALS AND METHODS

Childhood adrenocortical cancer cases were selected from the Children's Cancer Registry of Japan (Director: Dr. Noboru Kobayashi), and were found in the literature by a survey of the Japan Information Center of Science and Technology (JICST) data base. The Children's Cancer Registry of Japan covers about half of the incident cases of childhood cancers in Japan. Registered numbers of childhood cancer were 5,666 during 1969–1973, 5,929 during 1974–1978, and 6,785 during 1979–1983.[11] The JICST data base is maintained by the Agency of Science and Technology and contains more than 1.5 million references in medicine.

Thirty cases were found in the registry between 1969 and 1984, and 24 cases by JICST between 1965–1988. Seven cases were duplications. All cases in the literature were reported by clinicians, and two out of 24 were cases with multiple primary cancer; others were solitary cases reported mainly because of their rarity. The number of probands reported to the registry was 4 during 1969–

[1] A part of this work was presented at the 81st Annual Congress of the American Association of Cancer Research in 1990.

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1973, 6 during 1974–1978, 15 during 1979–1983, and 5 in 1984. The total number of probands was 47 after exclusion of duplicated cases. The numbers of cases in the literature were 3, 6, and 5 respectively, corresponding to the above three periods, and 3 during 1984–1988.

Diagnosis of adrenocortical carcinoma of probands had been confirmed by surgical pathology and/or autopsy. Pathology reports were reviewed, if possible, but a review of glass slides was not done.

Questionnaires were sent to the attending physicians in June 1989 to confirm the family pedigrees by collecting new incident cases of cancer since the first registry or report. Thirty-five out of 47 physicians (74.5%) responded, and up-to-date follow-up information was obtained from 25 of them. Telephone interviews were conducted for 22 pedigrees and present status was confirmed in 15 families. Family pedigrees of 12 non-respondants were used from the initial registry or report. The number of families providing follow-up information according to source is shown in Table I.

The proportions of histological types of cancers appearing under the age of 45 among family pedigrees were compared with those among the Japanese population and the US white population.[12, 13] Proportional incidence ratios for major cancers were calculated using the sex- and age- (0–44 years old) specific proportions of each cancer site. Confidence intervals (95%) for proportional incidence ratios were calculated according to the method of Breslow and Day.[14]

Frequency of cancer occurrence in the mother was compared separately with expected cancer occurrence calculated from the Japanese cancer incidence by site and sex.[12] The mothers' ages had not been filled out in 5 registry cases and 7 reported cases, so 35 mothers' ages were available for calculation. Observed/expected ratio was tested by Breslow's method.[14] Cumulative occurrence of cancers in mothers of 35 probands was calculated and tested by the Kaplan-Meier method.

RESULTS

The characteristics of the probands were as follows: male-to-female ratio of probands was 1:1.5, and average age at onset was 4.4 ± 3.2 in boys and 4.5 ± 3.0 in girls. Age distribution is shown in Fig. 1. Eleven proband cases were alive, 26 dead and 10 were lost to follow-up. Multiple cancer in the probands was recognized in 2 cases. One had triple primary cancer of synchronous adrenocortical carcinoma and neuroblastoma at age 7 months and rhabdomyosarcoma at age 4 years,[15] and another had adrenocortical carcinoma at age 11 months and osteosarcoma at age 15 years. Two cases showed hemihypertrophy and one showed overgrowth (+3.5 SD in height and bone age being 10 years at 5 years of age).

The numbers of responses to questionnaires and telephone interviews by the source of probands are shown in Table I. Follow-up information was obtained from 25 out of 30 probands in the registry series, and 10 out of 17 in the literature series. Information about cancer incidence was obtained for at least two generations.

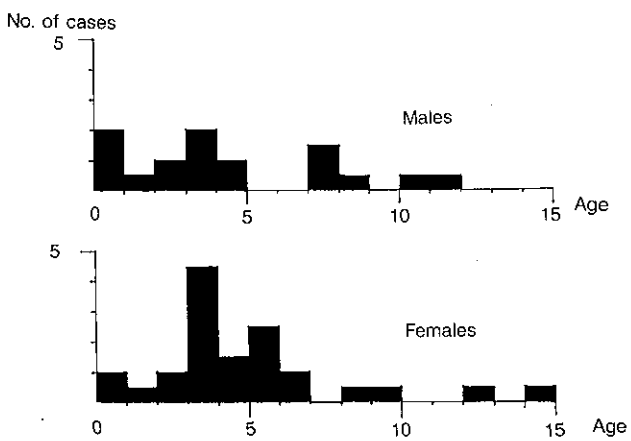

Fig. 1. Age distribution of probands by sex. Nineteen males and 29 females.

Table I. Follow-up Information by Source of Proband

	No. of proband	Response +	Follow-up information	Additional cancer <45 yr[a)]	Further additional cancer[b)]
Registry	30	25	17	6	3
Literature	17	10	9	3	1
Total	47	35	26	9	4

a) <45 yr, younger than 45 years of age.
b) Data obtained by telephone interview.

Table II. Number of Cancers by Site among Relatives of 47 Adrenocortical Cancer Cases

	Sarcoma	Brain	Lymphoma	Breast	Lung	Stomach	Liver	Uterus	Ovary	Others	Total
Proband	2*									1*	3
Sibling		1								1	2
Half sib			1				1				2
Father		1			2					1*	4
Mother				3	1	1			1		6
Grandfather						4				1	5
Grandmother				2	1	1		3			7
Uncle	1					1	1			3	6
Aunt				2				2	1		5
Cousin	1						2				3
Total	4	2	1	7	4	7	4	5	2	7	43

* Multiple primary cancer cases.

Table III. Number of Cancers by Age of Onset and Site among Families of Probands

	<15 yr	15–44 yr	>45 yr
Sarcoma	4	—	—
Brain tumor	1	1	—
Lymphoma	1	—	—
Breast	—	6	1
Lung	—	2	2
Stomach	—	5	2
Liver	3	1	—
Uterus	—	2	3
Ovary	—	2	—
Others	1	5	1
Total	10	24	9

The number of cancers among relatives had been 18 at the time of initial diagnosis of proband cases, but 27 additional incident cases were found by this survey. Thirty-four out of 43 (79%) occurred at the age of 45 or under. Frequently occurring cancers were of the breast, stomach, uterus and liver (Table II). Other cases included 1 colon cancer in a sibling, multiple cancer of the submandibular gland and lung in the father, rectum cancer in the grandfather and one each of cancer of the pancreas, bladder and nasopharynx in uncles.

The ages at diagnosis for these cancers in relatives were younger even for the more common cancers, such as of the stomach and liver (Table III). Two of the four liver cancers were hepatoblastoma. The proportions of these cancers were compared to those among the general populations in Japan and the USA (Table IV). A significantly higher proportional incidence of cancer was recognized in osteosarcoma and liver, and a higher frequency was suggested in the breast, brain and lung.

Breast cancer among mothers was further analyzed. Six mothers developed cancer (3 breast, 1 stomach, 1 lung and 1 ovary). Observed/expected ratio of mothers' cancer (all sites) was 15.4 (99% confidence interval (CI); 3.9–40.3), and O/E ratio of mothers' breast cancer was 50.3 (99% CI; 5.1–184.0). Cumulative probability of mothers' cancer occurrence in comparison with the general population in Japan is shown in Fig. 2.

Analysis of each family pedigree revealed that 7 families had 3 or more cancers within the first generation (Fig. 3). Only one family satisfied the original criteria of Li, in which 3 were childhood cancer cases including lymphoma and father's lung cancer at a young age of onset (Fig. 3a). The father of the proband case had married twice, and 3 of 4 children from two mothers had childhood cancers. Three of the father's 6 siblings had died of cancer, one of osteosarcoma. If the multiple primary cancers in the proband were counted as two cancers, two other families would be classified as having Li-Fraumeni syndrome (Fig. 3b, c). Four other families had 3 or more cancers within the first generation, but these families were characterized by a lack of sarcoma of mesenchymal origin (Fig. 3d–e).

DISCUSSION

Li-Fraumani syndrome resembles Lynch's SBLA syndrome in many respects, but the distribution of cancer is somewhat different (Table V). Li[6] set the criteria that 1) the proband may have any sarcoma which occurs at age less than 45, 2) among first-degree relatives, at least two of any cancers occur at less than 45 years of age, or 3) among first- or second-degree relatives, any cancer occurs at less than 45 years of age or sarcoma at any age.[6] He later revised the criteria to be that sarcoma at less than 45 years of age in the proband and cancers in

Table IV. Proportions of Cancers between Ages 0–44 Years in Families of Probands, Japanese and American General Populations

	This study		Japan	PIR (CI)	USA
	No.	%	1985		1980–1985
Soft tissue	1	2.9	1.2	2.41 (0.06–13.65)	2.0
Bone	3	8.8	0.9	9.77* (2.02–28.62)	1.2
Leukemia	0	0	6.7	—	5.5
Lymphoma	1	2.9	3.3	0.88 (0.02–4.96)	9.4
Brain tumor	2	5.9	4.2	1.40 (0.17–5.05)	5.0
Stomach	5	14.7	23.1	0.64 (0.21–1.49)	1.0
Colon	1	2.9	4.1	0.71 (0.02–4.01)	3.2
Liver	4	11.8	2.9	4.07* (1.10–10.39)	0.6
Pancreas	1	2.9	1.1	2.64 (0.07–14.87)	0.8
Lung	2	5.9	3.1	1.90 (0.23–6.86)	5.2
Breast	6	17.6	13.8	1.28 (0.47–2.79)	20.8
Others	8	23.5	35.5	0.66 (0.28–1.30)	45.0
Total	34	100.0	100.0		100.0

Proportion of cancer was calculated from Japanese incidences of cancer[12] and that of the SEER program[13] in 1985. PIR, proportional incidence ratio; CI, confidence interval; *, $P<0.05$.

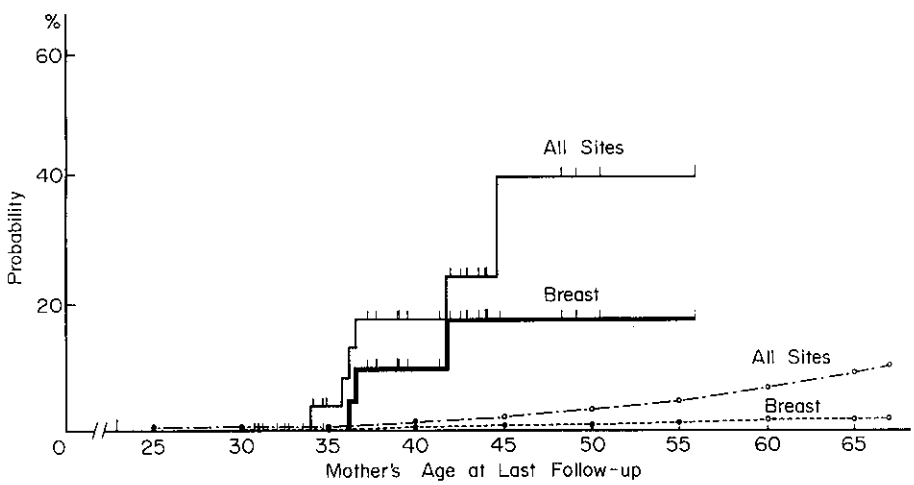

Fig. 2. Cumulative probabilities of cancer occurrence in mothers of 35 children with adrenocortical carcinoma. Dotted lines are expected occurrence of cancer calculated from the Japanese general population.

at least two young relatives should be present.[16] Breast cancer frequently occurring at a young age of onset and bilaterally, and osteosarcoma, brain tumor, leukemia, adrenocortical cancer recognized in one family would satisfy the revised criteria. He also accepted that multiple primary cancers may be equivalent to cancers in two members of a family. SBLA syndrome includes sarcoma, breast cancer, brain tumor, lung and laryngeal cancer, leukemia and adrenocortical carcinoma in family pedigree. Multiple primary cancer is also frequently found.[8]

We started with adrenocortical carcinoma as the proband, because it is included in both syndromes, and leukemia and sarcoma occur too commonly as tumors in childhood, which would dilute the genetically related accumulation of cancer. It is difficult to distinguish genetically determined cancer from common cancer if the proportion of inherited cancer is small. The frequency of adrenocortical carcinoma among all cancers at less than 45 years of age from the Annual of the Pathological Autopsy Cases in Japan (1975–1988) was 74 out of

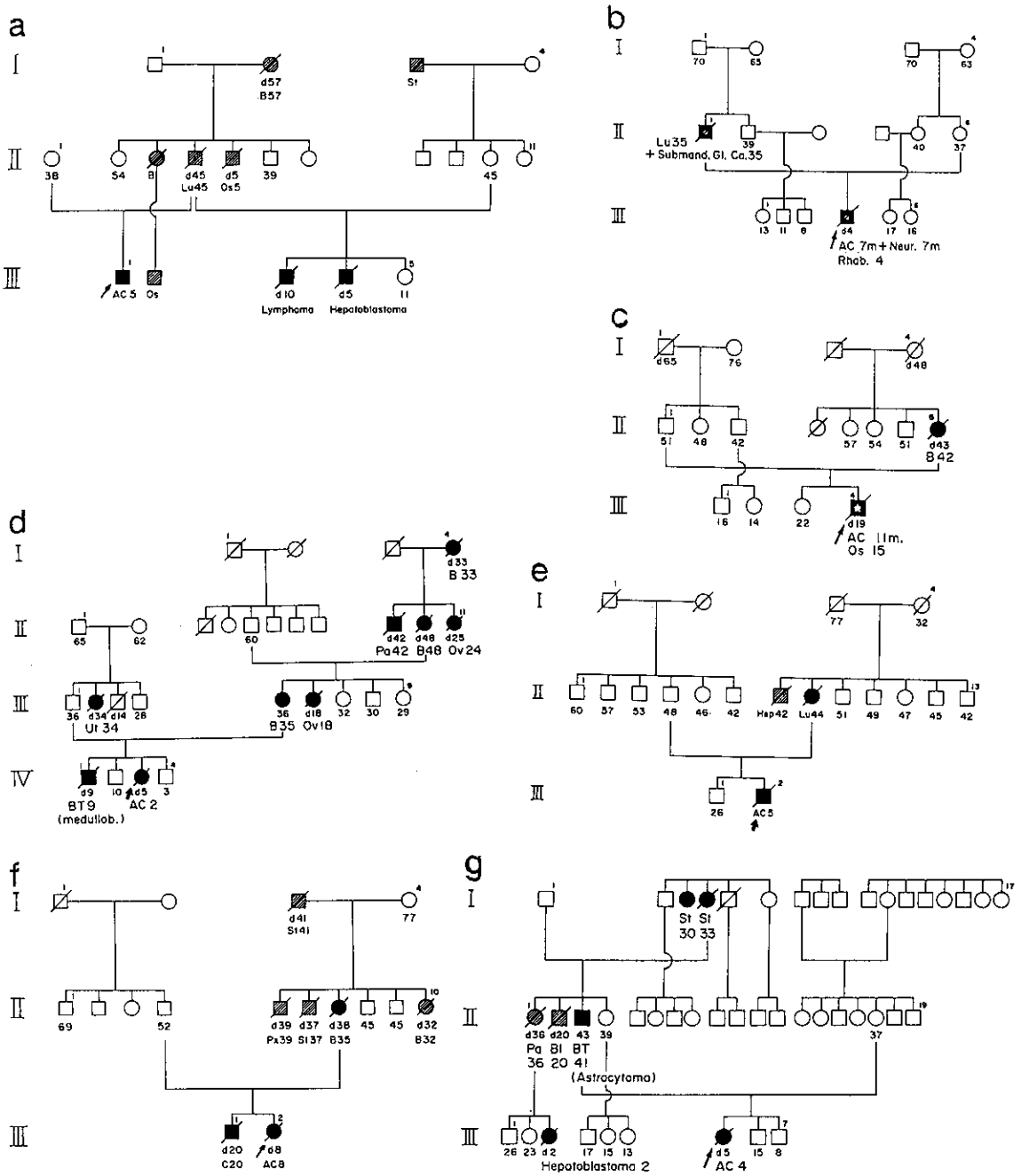

Fig. 3. Family pedigree of representative cases. a) Acceptable Li-Fraumeni syndrome: Father of proband case married twice, and 3 of 4 children from two mothers had childhood cancers. Three of 6 siblings of the father died of cancer, and one child of the father's sister died of osteosarcoma. b) Triple cancer in proband and father's double primary cancer. c) Multiple primary cancer in proband and mother's breast cancer with young onset may satisfy Li-Fraumeni criteria, but the penetration rate seemed to be low. d–g) There are aggregations of cancer, but no sarcoma of mesenchymal origin was involved. AC, adrenocortical carcinoma; B, breast cancer; BT, brain tumor; C, colon cancer; ST, stomach cancer; Lu, lung cancer; Lx, laryngeal cancer; Px, pharyngeal cancer; Pa, pancreas cancer; Ov, ovarian cancer; Ut, uterine cancer; Bl, bladder cancer; Rhab, rhabdomyosarcoma; Neur, neuroblastoma; Os, osteosarcoma; Hep, hepatoma; □, males; ○, females; ⊠⊘, deceased; 1,2, pedigree code; ■ ●, cancers verified by pathology; ◪, multiple primary cancers verified by pathology; ■ ●, cancers reported by family history; B48, cancer site (breast) and age, 48 years. Arrow; probands.

Table V. Criteria of Li-Fraumeni Syndrome and Lynch's SBLA Syndrome

	Li-Fraumeni syndrome	Lynch's SBLA syndrome
Proband	Any sarcoma <45 yr	
Criteria	Cancers in at least 2 young relatives	
Frequently occurring tumors	Breast, often at a young age and bilateral	Sarcoma
	Osteosarcoma	Breast
	Brain tumor	Brain
	Leukemia	Lung
	Adrenocortical cancer	Larynx
		Leukemia
		Adrenocortical cancer
	Multiple primary cancer	Multiple primary cancer

37,749 (0.20%), and there were only 17 cases under the age 15 years.[17]

The number of pedigrees which had more than two cancers in the first generation in addition to the proband case, occurring at less than 45 years of age, was 7 out of 47 (14.9%). Although 18 cases of cancer in the family pedigree were found among 47 families (38.3%) at the time of initial diagnosis of the proband case, twenty-seven new cancer cases (77.1% of total cancers among pedigrees) were found in the follow-up, demonstrating the importance of this kind of study.[18]

Penetration or expression rate of cancer gene(s) in Li-Fraumeni syndrome has not yet been clarified. Li's 24 families had been collected from cases in the Cancer Family Registry of the Epidemiology Branches at NCI, so the selection bias yielded a seemingly high penetration rate.[6] In this series, it seemed to be lower than that reported in the USA. Only one family is acceptable to be classified as Li-Fraumeni syndrome by the original criteria, and two others may be acceptable if multiple primary cancer of the proband may be counted as two. In these two family pedigrees, however, cancer was only present in the mother and child or father and child. Four other family pedigrees included more than 3 younger onset cancers within one generation, but a lack of sarcoma was characteristic.

Breast cancer was the cancer most frequently associated with childhood sarcoma.[19–23] In our series, however, 3 mothers out of 47 (6%) developed breast cancer. Four others were breast cancer in the grandmother or aunts. Although the incidence of breast cancer in Japan was about one-fourth of that in the USA in this age category,[24] the proportional cumulative incidence by age 45 was 1.6 times higher than that of the Japanese general population.

The frequency of adrenocortical carcinoma in Li-Fraumeni's series was about 10%. If this frequency could be applied to data from Japan, the number of families with genes related to this syndrome may be 10 times greater. On the contrary, family pedigrees starting with probands with sarcoma or leukemia could not be detected in 4 of these families. Four families showed a combination of rather common epithelial tumors, such as stomach, pancreas and colon cancer, at a young age of onset, in addition to brain and/or germ cell tumors. The validity of including germ cell tumors in Li-Fraumeni syndrome was proposed by Hartley *et al.*[25] Four of these families gave us the impression that they might belong to the intermediate type of Lynch's cancer family syndrome type I and type II. The alternative name of sarcoma-breast cancer syndrome, instead of Li-Fraumeni syndrome or SBLA (Lynch's type II) syndrome, seems to be somewhat premature, because of the presence of families such as those above and the low frequency of breast cancer in countries like Japan.

The mechanism of multiple occurrence of different cancers according to dominant heredity is not known. At present there is no consistent genotypic or phenotypic marker to identify individuals who carry this putative cancer-predisposing gene. Little *et al.*[26] examined radiation resistance of 6 cell strains from one family representing affected, nonaffected, and at-risk individuals and two strains from affected individuals from two other families, and found no difference in cytotoxic effects or production of chromosome aberrations by radiation.

Yano *et al.*[27] reported a loss of heterozygosity in human adrenocortical carcinoma at 17p (6/6), 11p (4/6), 13q (3/6), and one HRAS1 mutation (1/9). As benign tumors and hyperplasia did not show such chromosomal deletions (0/8), accumulated changes at tumor suppressor loci in particular organs could lead to the different histological types. Inactivation of several tumor suppressor genes and activation of oncogenes is considered to be essential for the development of malignancy.[28] Malkin *et*

al.[29] recently reported that point mutation is present in the p53 tumor suppressor gene in lymphocytes and/or fibroblasts of the patients of Li-Fraumeni syndrome. Two of our cases also had p53 gene alteration (Yokota *et al.*, in preparation). Further linkage studies on families with DNA changes would be desirable from a molecular epidemiological viewpoint.

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